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Combined Low Dose Dipyridamole-Dobutamine Stress Echocardiography to Identify Myocardial Viability

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Objectives. **We sought to evaluate the effects of combined administration of infra-low dose dipyridamole and low dose dobutamine on assessment of myocardial viability.**

Background. **Low dose pharmacologic stress echocardiography with either dobutamine or dipyridamole infusion has been proposed for the recognition of myocardial viability.**

Methods. **Thirty-four patients with rest wall motion dyssynergy by two-dimensional echocardiography and with angiographically proved coronary artery disease underwent in combination with two-dimensional echocardiographic monitoring: 1) low dose (5 to 10 μg/kg per min over 3 min) dobutamine infusion; 2) infra-low dose (0.28 mg/kg over 4 min) dipyridamole infusion; 3) combination of infra-low dose dipyridamole infusion immediately followed by low dose dobutamine infusion (combined dipyridamole-dobutamine).**

Results. **Follow-up rest echocardiography was available in 30 patients. After revascularization, 82 segments showed a contractile improvement of ≥1 grade, whereas 63 segments remained unchanged. The sensitivity of dobutamine, dipyridamole and combined dipyridamole-dobutamine for predicting recovery was 72% (95% confidence interval [CI] 60.9% to 81.3%), 67% (CI 55.8% to 77%) and 94% (CI 86.3% to 97.9%), respectively. The specificity of dipyridamole, dobutamine and combined dipyridamole-dobutamine was 95% (CI 86.7% to 99%), 92% (CI 82.4% to 97.3%) and 89% (CI 78.4% to 95.4%), respectively. The accuracy of the dobutamine, dipyridamole and combined dipyridamole-dobutamine test was 80%, 79% and 92%, respectively (combined dipyridamole-dobutamine vs. dobutamine, $p < 0.05$; combined dipyridamole-dobutamine vs. dipyridamole, $p < 0.01$).**

Conclusions. **Infra-low dose dipyridamole added to low dose dobutamine recruits an inotropic reserve in asynergic segments that were nonresponders after either dobutamine or dipyridamole alone and destined to recover after revascularization.**

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The identification of viable myocardium has been recognized as an increasingly important goal in clinical cardiology (1–3). The potential reversibility of myocardial dysfunction in certain settings is now well established, but a remaining challenge is the development of an accurate means of reliably distinguishing reversible from irreversible dysfunction (4–7). Low dose dobutamine stress echocardiography is an attractive and increasingly used method of identifying viable myocardium based on its ability to respond to beta-adrenergic stimulation with an increase in myocardial thickening (8–14). The specificity of low dose dobutamine stress echocardiography for predicting functional recovery is excellent, but its sensitivity is less than ideal. Thus, a segment that shows improved wall motion with dobutamine, is likely to be viable and to recover with revascularization; but viability is still possible even if wall motion does not improve with dobutamine.

Experimental (15,16) and clinical (17,18) studies have shown that coronary vasodilator stress can recruit an inotropic reserve in viable segments. In particular, the infra-low dipyridamole dose regimen designates a dosage (0.28 mg/kg in 4 min) that selectively explores myocardial viability and has virtually no ischemic potential (18). This viability dose is called "infra-low" because it is 50% lower than the regular or low dose (0.56 mg/kg in 4 min), originally proposed by Gould (19) and currently employed in perfusion imaging, and 67% lower than the high dose (0.84 mg/kg in 10 min) most frequently used for echocardiographic imaging when myocardial ischemia is the diagnostic end point (20,21). Therefore, in patients with chronic coronary artery disease, a theoretically attractive way of increasing the sensitivity of pharmacologic stress echocardiography would be the addition of infra-low dose dipyridamole to low dose dobutamine. The two agents act through different, potentially synergic mechanisms: Dobutamine is a mild $beta_1$-adrenoreceptor–mediated inotropic stimulus on the myocardium, secondarily increasing coronary flow (22), whereas dipyridamole is an adenosine A_2-receptor–mediated mild vasodilator stimulus on the coronary arterioles, secondarily

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increasing myocardial function (15,16). The combined dipyridamole-dobutamine stress for viability should also be safe, because substantially higher doses of both dipyridamole and dobutamine have been used in a single combined test for the diagnosis of coronary artery disease (23), with excellent accuracy and tolerability.

We therefore separately performed infusions of low dose dobutamine alone, infra-low dose dipyridamole alone and combined infra-low dose dipyridamole and low dose dobutamine in 34 consecutive patients referred to the echocardiography laboratory for assessment of myocardial viability. All patients underwent a revascularization procedure; echocardiographic follow-up after a successful revascularization was obtained in 30 patients. Our working hypothesis was that the combined infra-low dose dipyridamole and low dose dobutamine stress would have greater sensitivity in identifying myocardial viability than would stress with either dipyridamole or dobutamine alone.

Methods

Study patients. Fifty-one consecutive patients with a history of myocardial infarction, angiographically proved coronary artery disease, a technically satisfactory acoustic window and wall motion dyssynergy of the left ventricle at rest were initially considered. Of these 51 patients, 17 underwent the stress echocardiographic study but did not enter the echocardiographic follow-up program because they did not undergo coronary revascularization on the basis of the independent decision of the referring physician. As in any other patient with coronary artery disease, this decision was based on clinical presentation, coronary anatomy and evidence of inducible ischemia in addition to assessment of myocardial viability, which was not in itself an indication for revascularization.

Of the initial group of 51 patients, 34 (30 men and 4 women, age range 31 to 73 years [mean ± SD 55 ± 11]) underwent revascularization and were enrolled in the study (Table 1). All 34 patients had evidence of previous (>3 months) myocardial infarction. Twenty-two patients had a Q wave infarction and 12 had a non-Q wave infarction. The site of the Q wave infarction was anterior in 12 patients and inferior in 10. Medical therapy was discontinued ≥48 h before the stress echocardiographic examination in 18 patients; the other 16 patients were examined while receiving antianginal therapy: nitrates in 1 patient beta-adrenergic blocking agents in 2 and combined therapy in 13 (nitrates and calcium antagonists in 9, nitrates and beta-blockers in 3 and triple therapy [nitrate plus calcium antagonist plus beta-blocker] in 1). Coronary angiography demonstrated significant stenosis (≥50% diameter reduction by quantitative coronary angiography) of one vessel in 18 patients, of two vessels in 10 and of three vessels in 6. Average left ventricular ejection fraction calculated from the apical four-chamber view by two-dimensional echocardiography (single-plane area-length method) was 43 ± 12%. Coronary revascularization was performed in all 34 patients either by coronary artery bypass surgery (n = 9) or by percutaneous transluminal coronary angioplasty (n = 25). Of the 34 patients submitted to revascularization and entered in the follow-up program, 4 (Patients 31 to 34) were subsequently excluded from follow-up because coronary revascularization was unsuccessful. Of these four patients, two died in the perioperative period, one had early restenosis (within 1 month) and one had a perioperative reinfarction complicated by ventricular fibrillation. A baseline follow-up echocardiogram obtained at least 4 weeks (mean 7 ± 3) after revascularization was available in 30 patients. None of these patients showed clinical, enzymatic, electrocardiographic (ECG) or echocardiographic evidence of a perioperative myocardial infarction, and all were thought to have had successful revascularization, because they were asymptomatic and had fully negative results on functional tests of ischemia, including maximal high dose pharmacologic stress echocardiography.

Baseline echocardiographic examination. Two-dimensional echocardiograms were obtained by using commercially available imaging systems (Hewlett-Packard Sonos 1000, 1500 or 2000 or Diasonics 2.5- and 3.5-MHz transducers). Echocardiographic images were recorded on VHS videotape for subsequent playback and analysis. Regional wall motion was assessed according to the recommendations of the American Society of Echocardiography (24) with a 16-segment model. In all studies, segmental wall motion was semiquantitatively graded as follows: normal = 1; hypokinetic, marked reduction of endocardial motion and thickening = 2; akinetic, virtual absence of inward motion and thickening = 3; and dyskinetic, paradoxic wall motion away from the center of the left ventricle in systole = 4. A wall motion score index was derived by dividing the sum of individual segment scores by the number of interpretable segments. Baseline echocardiography was performed before coronary angioplasty or coronary artery bypass surgery. Inadequately visualized segments were not scored.

Pharmacologic stress echocardiography. All patients underwent, in separate sessions and before coronary revascularization, low dose dobutamine infusion (5 μg/kg per min followed by 10 μg/kg per min, each stage lasting 3 min); infra-low dose dipyridamole (0.28 mg/kg over 4 min); infra-low dose dipyridamole followed by low dose dobutamine echocardiography (Fig. 1). Two-dimensional echocardiograms were continuously obtained and intermittently recorded during drug administration. In the baseline studies as well as during stress, all standard echocardiographic views were obtained when possible. During the procedure, the blood pressure and the ECG were recorded each minute. Off-line assessment of echocardiographic images was performed by two experienced independent investigators unaware of the clinical, angiographic and follow-up data. When there was disagreement between the two readers, which occurred in at least one segment in three patients, a third investigator reviewed the images without knowledge of the previous assessment and a consensus decision was achieved. Interobserver agreement regarding the presence or absence of myocardial viability in a segment by segment assessment was 92%. The low level of interobserver variability between experienced observers in our

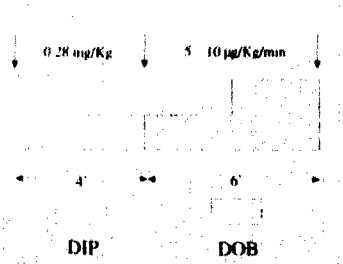
Table 1. Clinical, Echocardiographic and Angiographic Features of the 34 Study Patients

Pt No.	Age (yr)/ Gender	Previous Infarction	Dyssynergic Area	Coronary Angiography (% stenosis)				Wall Motion Score Index						Vessel Revascularized
				LMCA	LAD	LCx	RCA	Baseline	DOB	DIP	Combined DIP-DOB	Ischemia	FU	
1	51/M	Q	Inferobasal	0	75	100	0	1.38	1.38	1.38	1.38	None	1.38	LAD,LCx
2	48/M	Q	Anteroseptal	0	90	0	0	1.38	1.13	1.13	1.06	None	1.13	LAD
3	56/F	Q	Inferobasal	0	0	0	90	1.31	1.31	1.31	1.31	None	1.31	RCA
4	58/M	Q	Anteroseptal	0	100	0	75	1.63	1.5	1.63	1.38	None	1.38	LAD
5	71/M	Q	Posterolateral	0	0	100	90	1.94	1.81	1.94	1.81	None	1.94	RCA
6	62/M	Q	Posterolateral	0	50	90	0	1.44	1.25	1.31	1.19	None	1	LCx
7	47/M	Non-Q	Anteroseptal	0	90	90	0	1.38	1.13	1.18	1	None	1.06	LAD
8	68/M	Q	Posterolateral	75	100	100	100	2	2	2	1.81	None	1.75	LAD,LCx,RCA
9	51/M	Non-Q	Posterior	0	0	0	90	1.25	1	1	1	None	1	RCA
10	61/M	Q	Apical	0	70	0	0	1.81	1.81	1.81	1.81	None	1.81	LAD
11	53/M	Non-Q	Apical	0	90	0	0	1.38	1	1	1	None	1.13	LAD
12	43/M	Q	Posterior	0	0	90	0	1.13	1	1	1	None	1	LCx
13	35/M	Q	Inferior	0	75	0	75	1.38	1.38	1.38	1.25	None	1.25	RCA
14	59/M	Q	Apicoseptal	0	90	0	0	1.63	1.5	1.56	1.5	None	1.38	LAD
15	48/M	Q	Apical	0	90	0	0	1.63	1.63	1.63	1.63	None	1.63	LAD
16	65/M	Q	Anteroseptal	0	90	0	0	1.81	1.63	1.63	1.63	None	1.63	LAD
17	58/M	Q	Posterior	0	0	0	95	1.25	1	1	1	None	1	LAD
18	71/M	Non-Q	Apical	0	90	0	0	1.31	1	1	1	None	1	RCA
19	68/M	Non-Q	Anterolateral	0	100	99	0	1.88	1.88	1.88	1.88	None	1.88	LAD,LCx
20	44/M	Non-Q	Apical	0	90	0	0	1.13	1.06	1	1	None	1	LAD
21	64/M	Non-Q	Apical	0	90	0	0	1.06	1.06	1.06	1	None	1	LAD
22	50/M	Non-Q	Posterior	0	0	0	90	1.13	1	1	1	None	1	RCA
23	45/M	Q	Apicoseptal	0	100	0	100	1.44	1.44	1.44	1.25	None	1.44	LAD,LCx
24	46/M	Q	Anteroseptal	0	100	99	0	1.31	1	1	1	None	1	LAD,RCA
25	64/M	Q	Apicoseptal	0	90	75	90	1.5	1	1.38	1.31	None	1.19	LAD,RCA,LCx
26	36/M	Non-Q	Posterior	0	0	75	75	1.38	1.06	1.06	1	None	1	RCA
27	46/M	Q	Apicoseptal	0	0	90	0	1.5	1.31	1.31	1.31	None	1.31	LCx
28	73/M	Q	Anteroseptal	0	90	90	90	1.44	1.44	1.44	1.25	None	1	LAD
29	52/M	Q	Anteroseptal	0	100	90	75	1.88	1.88	1.88	1.88	None	1.88	LAD,RCA,LCx
30	51/M	Non-Q	Apicoseptal	0	100	0	0	1.31	1	1	1	None	1	LAD
31	72/F	Non-Q	Apical	0	100	90	75	1.25	1.06	1.06	1	1.31	No	LAD,RCA,LCx
32	66/F	Q	Posteroinferior	75	90	0	100	1.81	1.63	1.63	1.63	1.88	No	LAD,RCA,LCx
33	65/M	Non-Q	Anteroseptal	0	100	0	0	1.63	1.5	1.63	1.31	None	No	LAD
34	31/F	Q	Anteroseptal	0	100	0	0	1.63	1.19	1.13	1.13	None	No	LAD

DIP = infra-low dose dipyridamole; DOB = low dose dobutamine; F = female; FU = follow-up; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; M = male; Non-Q = Non-Q wave; Pt = patient; Q = Q wave; RCA = right coronary artery.

laboratory has been documented (25) and is probably linked to previous extensive experience in joint reading and development of a priori reading criteria, thus overcoming the otherwise more substantial variability between independent "expert" readers (26). Digital acquisition of images of interest was obtained with a side by side display of rest and peak stress images in a cine-loop mode either on line or off line by an array-processor-based computer for medical image processing (Mipron, Kontron). A wall motion score index was derived for rest and peak stress echocardiograms (0 to 1 min after the end of each infusion) in all patients, as previously described for the baseline echocardiographic examination. A segment was considered to show signs of viability when it improved by ≥1 grade at peak stress (for instance, a hypokinetic segment becoming normal or an akinetic segment becoming hypokinetic).

Figure 1. Protocol of the combined infra-low dose dipyridamole (DIP)–low dose dobutamine (DOB) test. BP = blood pressure; ECG = electrocardiogram; 2D Echo = two-dimensional echocardiography.



Echocardiographic follow-up. Postoperative rest wall motion score was determined by two experienced echocardiographers who had no knowledge of stress echocardiographic results. Digital acquisition of images was obtained with a side by side display of echocardiograms obtained at baseline (before revascularization) and at follow-up (after revascularization). Improved segmental wall motion at follow-up was defined as endocardial excursion and wall thickening (score 1 or 2) in areas of akinesia or dyskinesia (score 3 or 4) at baseline, or normalization (score 1) of reduced endocardial excursion and wall thickening (score 2) at baseline.

Statistical analysis. Values are expressed as mean value ± SD. Differences in hemodynamic values before and after the infusions and in wall motion score index under different conditions were tested for significance by analysis of variance and subgroup analysis by the Newman-Keuls test. Calculations of sensitivity, specificity and accuracy were performed according to standard definitions and are reported with the corresponding 95% confidence interval (CI). Differences in the sensitivity, specificity and accuracy of the different tests were evaluated with the chi-square test. A p value < 0.05 was considered statistically significant.

Results

The main clinical, echocardiographic and angiographic features of the 34 study patients are reported in Table 1.

Baseline echocardiographic findings. By inclusion criteria, all patients had a regional dyssynergy in the rest echocardiogram. There were 168 segments with baseline dyssynergy: dyskinesia in 6, akinesia in 83 and marked hypokinesia in 79.

Clinical and hemodynamic findings during pharmacologic stress. None of the 34 patients had significant side effects or showed echocardiographic or ECG signs of ischemia after either dipyridamole or dobutamine infusion. However, in two patients a biphasic pattern (improvement of function followed by subsequent deterioration) and ECG changes were observed after the combined infra-low dose dipyridamole and low dose dobutamine stress. These two patients (Patients 32 and 33) were not included in the final analysis because they were among the four who had no follow-up echocardiographic study as a result of unsuccessful revascularization. The systemic hemodynamic findings—blood pressure, heart rate—in baseline conditions and during the pharmacologic stress tests are shown in Table 2. In comparison with the baseline value, systolic blood pressure increased slightly after dobutamine (p = NS) but did not change significantly after dipyridamole or dipyridamole-dobutamine. No test affected significantly diastolic blood pressure. Heart rate was also unchanged after dobutamine or dipyridamole alone, whereas a mild increase was observed after the combined dipyridamole-dobutamine stress.

Echocardiographic findings. Twenty-seven patients showed improved segmental wall motion during pharmacologic stress testing, whereas in seven patients no contractile reserve could be identified. Improvement in wall motion occurred in the distribution of the vessel that was bypassed or dilated. Wall motion score index was 1.48 ± 0.25 at rest and it improved significantly after dobutamine (1.33 ± 0.32, $p < 0.05$ vs. rest), after dipyridamole (1.34 ± 0.32, $p < 0.05$ vs. rest, p = NS vs. dobutamine) and after combined infra-low dose dipyridamole and low dose dobutamine stress (1.29 ± 0.3, $p < 0.05$ vs. rest, p = NS vs. dobutamine and vs. dipyridamole).

Table 2. Hemodynamic Changes During Stress Echocardiographic Testing

	Baseline	DOB	DIP	Combined DIP-DOB
Systolic blood pressure (mm Hg)	134 ± 19	140 ± 22	134 ± 17	135 ± 20*
Diastolic blood pressure (mm Hg)	77 ± 13	78 ± 17	76 ± 14	74 ± 16†
Heart rate (beats/min)	70 ± 11	73 ± 13	72 ± 12	78 ± 15†

*p = NS, †$p < 0.01$ versus baseline, dobutamine and dipyridamole.

Follow-up rest echocardiography. Follow-up echocardiographic examination after successful coronary revascularization was available in 30 patients (Table 1). At baseline echocardiography at study entry, these 30 patients showed a total of 145 dyssynergic segments. Regional wall motion improved in time by ≥1 grade in 82 segments ("viable"), whereas in the remaining 63 ("necrotic") no improvement could be observed. Of the 82 viable segments, dobutamine and dipyridamole correctly identified 59 and 55 segments, respectively, whereas combined infra-low dose dipyridamole and low dose dobutamine stress test identified 77. Of the 63 necrotic segments, dobutamine, dipyridamole and combined dipyridamole-dobutamine correctly identified 58, 60, and 56 segments, respectively. The sensitivity of dobutamine and dipyridamole was 72% (CI 60.9% to 81.3%) and 67% (CI 55.8% to 77%, respectively, p = NS). However, with the introduction of the combined method the sensitivity markedly improved to 94% (CI 86.3% to 97.9%, $p < 0.01$ vs. dobutamine and vs. dipyridamole). The specificity of dipyridamole and dobutamine was 95% (CI 86.7% to 99%) and 92% (82.4% to 97.3%), respectively and decreased to 89% (CI 78.4% to 95.4%) for combined dipyridamole-dobutamine stress (p = NS). The accuracy of the dobutamine, dipyridamole and combined dipyridamole-dobutamine stress test in predicting the behavior of the basally dyssynergic myocardial segment after revascularization was 80%, 79% and 92%, respectively (combined dipyridamole-dobutamine = $p < 0.05$ vs. dobutamine and $p < 0.01$ vs. dipyridamole) (Fig. 2). After revascularization 22 patients had improved segmental wall motion, and in 4 of these it was correctly predicted only by the combined dipyridamole-dobutamine stress test.

Discussion

Our results are in agreement with data from previous clinical studies (8–14) showing that ventricular dysfunction of viable tissue can be improved by an inotropic stimulus with an

accuracy of ~80% in predicting functional recovery after revascularization. In addition, the present study demonstrates the feasibility, tolerability and accuracy of a combined infra-low dose dipyridamole and low dose dobutamine regimen for selective assessment of myocardial viability, as well as its superior accuracy versus that either stress separately performed for predicting functional recovery. This finding has potential pathophysiologic and clinical relevance.

Mechanism of viability recognition by dipyridamole and dobutamine. The rationale of applying combined infra-low dose dipyridamole and low dose dobutamine as an effective stimulus for myocardial viability recognition stems from two assumptions: 1) infra-low dose dipyridamole is capable of recruiting contractile reserve in an asynergic but viable segment; 2) infra-low dose dipyridamole has an at least partially independent and additive effect to low dose dobutamine in recruiting inotropic reserve in a basally dyssynergic region.

Infra-low dose dipyridamole as a test for viability. In a dog model of stunned myocardium, Jeremy et al. (27) showed that a significant improvement in percent systolic thickening in the stunned area was achieved with very low adenosine doses, and the same improvement was obtained with adenosine doses up to 100 times higher. Their observation might explain why the inotropic reserve can be recruited with a similar efficacy by low and high doses of dipyridamole (17,18) whereas the ischemic effect increases sharply with increasing doses (21).

Infra-low dose dipyridamole can recruit an inotropic reserve through two possible mechanisms: hemodynamic (linked to increased coronary flow) or metabolic (due to accumulation of endogenous adenosine). Dipyridamole may increase postischemic function by increasing flow through the Gregg phenomenon (28): Changes in vascular distension affect sarcomere length and thereby influence contractile function (29). This interpretation is consistent with experimental (30,31) and clinical (32) studies demonstrating that a residual flow reserve can be elicited in the presence of a severe coronary stenosis and depressed baseline function. In addition, studies using myocardial contrast echocardiography (33) and positron emission tomography (34) have recently shown that the presence of a residual coronary reserve after dipyridamole infusion identifies segmental viability in patients with wall motion abnormalities at rest. The second, probably more likely, mechanism does not need the increase in coronary flow as the requisite of functional improvement. In an experimental study in a dog model of stunned myocardium, Zughaib et al. (35) showed that the augmentation of endogenous adenosine attenuates myocardial stunning independently of coronary flow or hemodynamic effects. This conclusion is corroborated by the study of Ely et al. (36), who reported beneficial effects of adenosine on ischemia-reperfusion injury in isolated hearts at constant coronary flow. Several flow-independent beneficial effects of endogenous adenosine have been hypothesized (37), including blocking of slow calcium channels (with reduction of cytosolic accumulation of calcium), glycolysis stimulation and inhibition of generation of free radicals.

Additive effect of dipyridamole and dobutamine. No direct experimental data support the additive inotropic action of dipyridamole and dobutamine in viable segments. However, in theory, dipyridamole and dobutamine might have potentially synergic actions because they act on different cellular and molecular targets: beta$_1$-adrenoreceptor of the myocyte for dobutamine, adenosine A_2 receptor of the coronary arteriolar smooth muscle cell for dipyridamole. In addition, administration of high dose dipyridamole does not block the hemodynamic response and potentiates the ischemic strength of high dose dobutamine (23). Furthermore, in a swine model of chronic reduction in perfusion pressure and flow, Mills et al. (38) showed that at baseline, regional myocardial blood flow distal to the stenosis was reduced in both endocardial and epicardial layers in comparison with levels in the normal zone. Transmural flow increased a mean of 280% from baseline in response to adenosine plus phenylephrine but only ~50% in response to adenosine alone. Because the increase in flow is accompanied by an increase in function in both stunned and hibernating myocardium (6), the experimental data of Mills et al. may provide indirect support for our empirical finding that dipyridamole and dobutamine have at least partially additive effects in eliciting a contractile response in viable myocardium.

Study limitations. One limitation of our study is the use of echocardiographically documented improvement of wall motion at follow-up as the criterion for judging the accuracy of stress-induced functional improvement. We did not use an independent standard such as fluorodeoxyglucose or thallium uptake. In addition, an angiographic control study was not performed at the time of follow-up examination. Some segments that did not recover might have been perfused by

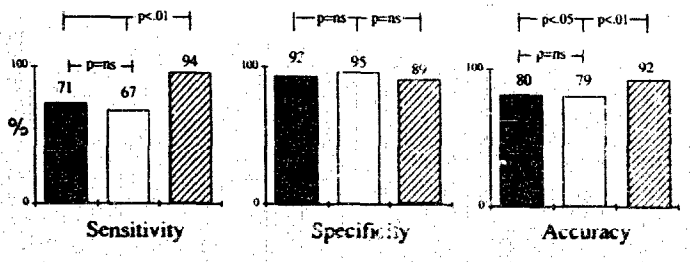


Figure 2. Bar graphs showing sensitivity, specificity and accuracy of dobutamine, dipyridamole and combined infra-low dose dipyridamole and low dose dobutamine test for myocardial viability assessment (gold standard: functional recovery). The combined dipyridamole-dobutamine test results in a significant increase in sensitivity and accuracy without a decrease in specificity compared with the results achieved with separate administration of either dipyridamole or dobutamine. **Solid bars** = dobutamine; **open bars** = dipyridamole; **hatched bars** = dipyridamole + dobutamine.

coronary arteries that had reoccluded, thereby leading to an underestimation of the test's specificity for predicting viability. Nevertheless, the specificity was excellent for dobutamine, dipyridamole and combined infra-low dose dipyridamole and low dose dobutamine, suggesting that this potential problem did not play an important role in the study patients. In addition, all patients were asymptomatic at follow-up and had negative results on functional tests of ischemia (maximal high dose pharmacologic stress echocardiography), suggesting persisting vessel patency in these patients.

The ideal pharmacologic stress for selective myocardial viability assessment should be hemodynamically neutral, with no effect on heart rate or systolic blood pressure, because manipulation of hemodynamic variables can induce variations in wall motion and thickening independently of the local inotropic effect. In addition, the test should not induce ischemia, as this may obscure the assessment of functional recovery. The combined infra-low dose dipyridamole and low dose dobutamine stress slightly deviates from this ideal profile, because it induced a significant, although mild, increase in blood pressure and induced ischemia in two patients who had tolerated well separately administered infusions of dipyridamole and dobutamine.

The study group included a substantial number of patients with only mild left ventricular impairment (average ejection fraction 43 ± 12%). With completion of the present initial feasibility study, the combined infra-low dose dipyridamole and low dose dobutamine test should be assessed in patients with severe left ventricular dysfunction, in whom the clinical question regarding the extent of viable tissue is more important. This validation is currently ongoing on a multicenter basis, with the VIDA (Viability Identification with Dipyridamole-Dobutamine Administration) project.

Clinical implications. It is generally agreed that either stress-redistribution-reinjection or rest-redistribution thallium protocols may provide cost-effective information regarding myocardial viability in the majority of patients with chronic ischemic left ventricular dysfunction (4). More recently, pharmacologic stress echocardiography has gained increasing acceptance, because of its low cost, widespread availability and use of nonionizing energy, in spite of the recognized limitations of ultrasound technology of depending on patient's acoustic window and observer expertise (39). A more substantial limitation of stress echocardiography is the less than ideal sensitivity in predicting functional recovery after revascularization. The present study shows that combined infra-low dose dipyridamole-low dose dobutamine increases the diagnostic accuracy of low dose dobutamine stress echocardiography, providing a critical stepup in sensitivity, without loss in specificity, with potential to make pharmacologic stress echocardiography even more attractive for detection of myocardial viability.

As a potential limitation of the test, one should consider that direct drug costs, preparation time and imaging time are obviously greater with combined infra-low dose dipyridamole and low dose dobutamine than with either drug separately used. However, when compared with dobutamine alone, the imaging time is increased by only 4 min (up to a total imaging time of 10 min). The preparation time in only trivially increased because the same intravenous line is used for serial administration of dipyridamole and dobutamine. The incremental cost of adding the infra-low dose dipyridamole varies substantially in the various countries. In Italy, the drug cost of 20 mg of dipyridamole (the average low dose in a 70-kg person) is <$1 US. Altogether, the combined test seems to be a user-friendly, non-time-consuming and cost-effective option toward an efficient diagnosis of myocardial viability with pharmacologic stress echocardiography.

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